AMENDMENTS TO THE CLAIMS

This listing replaces all prior versions and listings of claims in the application.

Listing of Claims

1. (Currently amended) A method for determining the type of biocompatible polymer, the extent of modification, and the conditions for modification of a therapeutic agent with a biocompatible polymer to prevent host-mediated inactivation of said therapeutic agent when covalently modified by said biocompatible polymer, comprising:

(a) assaying **a first blood sample for** a biological activity of a first modified therapeutic agent after said first modified therapeutic agent has been administered to ~~a~~ **an immunocompetent** subject, wherein said first modified therapeutic agent is covalently modified with a biocompatible polymer;

(b) assaying **a second blood sample for** the biological activity of said first modified therapeutic agent after at least one booster dose of said first modified therapeutic agent has been administered to said subject;

(c) assaying **a third blood sample for** the biological activity of a second modified therapeutic agent after said second modified therapeutic agent has been administered to ~~a~~ **an immunocompetent** subject, wherein said second modified therapeutic agent is covalently modified with a biocompatible polymer and wherein at least one condition selected from the group consisting of the type of biocompatible polymer, the extent of modification, and the conditions for modification differs from the conditions of said first modified therapeutic agent;

(d) assaying **a fourth blood sample for** the biological activity of said second modified therapeutic agent after at least one booster dose of said second modified therapeutic agent has been administered to said subject; and

(e) comparing the biological activity of said first modified therapeutic agent with the biological activity of said second modified therapeutic agent to select the type of biocompatible polymer, the extent of modification, and the conditions for modification that

prevent host-mediated inactivation of said therapeutic agent when covalently modified by said biocompatible polymer,

wherein said blood samples are collected from said immunocompetent subject,

wherein said biological activity is selected from the group consisting of an enzyme catalyzing a reaction, a molecule binding a receptor or antibody, mediating a receptor-mediated response such as ion influx/efflux or generation of second messengers, antagonizing or blocking a receptor-mediated response, induction of apoptosis and release or uptake of a neurotransmitter or hormone, and

wherein said assaying comprises measuring the extent to which said first modified therapeutic agent and said second modified therapeutic agent catalyze a reaction, bind a targeted receptor or antibody, or mediate activity of a receptor.

2. (Previously Presented) The method of claim 1, wherein said second modified therapeutic agent is modified with the same biocompatible polymer as said first modified therapeutic agent.

3. (Previously Presented) The method of claim 2, wherein said biocompatible polymer is polyethylene glycol (PEG).

4. (Original) The method of claim 3, wherein said PEG is selected from the group consisting of mono-methoxy succinimidyl butanoate (SBA)-PEG, succinimidyl carbonate (SC)-PEG, aldehyde (ALD)-PEG, and succinimidyl propionate (SPA)-PEG.

5. (Previously Presented) The method of claim 1, wherein said second modified therapeutic agent is modified to the same extent as said first modified therapeutic agent.

6. (Previously Presented) The method of claim 1, wherein said second modified therapeutic agent and said first modified therapeutic agent are modified with different biocompatible polymers.

7. (Previously Presented) The method of claim 1, wherein said therapeutic agent comprises a polypeptide.

8. (Original) The method of claim 7, wherein said polypeptide is used to treat viral infections in patients in need of treatment thereof.

9. (Original) The method of claim 7, wherein said polypeptide is used to treat cancer in patients in need of treatment thereof.

10. (Original) The method of claim 7, wherein said polypeptide has a monomeric molecular weight of about 300 daltons to about 300,000 daltons.

11. (Original) The method of claim 7, wherein said polypeptide is used to lower glutamine levels in a subject.

12. (Original) The method of claim 7, wherein said polypeptide is used to lower asparagine levels in a subject.

13. (Original) The method of claim 7, wherein said polypeptide is used to lower asparagine and glutamine levels in a subject.

14. (Withdrawn) The method of claim 1, wherein said therapeutic agent is a nucleic acid.

15. (Withdrawn) The method of claim 14, wherein said nucleic acid is used to treat a viral infection in patients in need of treatment thereof.

16. (Withdrawn) The method of claim 14, wherein said nucleic acid is used to treat cancer in patients in need of treatment thereof.

17. (Previously Presented) A method of preparing a pharmaceutical composition where host-mediated inactivation is prevented, comprising selecting the type of biocompatible polymer, the extent of modification, and the conditions for modification of a therapeutic agent by the method of claim 1 and modifying said therapeutic agent according to

the type of biocompatible polymer, the extent of modification, and the conditions for modification selected.

18. (Original) The method of claim 17, wherein said pharmaceutical composition further comprises an excipient.

19. (Original) The method of claim 18, wherein said excipient protects said therapeutic agent during lyophilization.

20. (Original) The method of claim 17, wherein said therapeutic agent comprises glutaminase-asparaginase.

21. (Previously Presented) The method of claim 20, wherein said therapeutic agent comprises *Pseudomonas* glutaminase-asparaginase.

22. (Original) The method of claim 21, wherein said *Pseudomonas* glutaminase-asparaginase is modified with polyethylene glycol.

23. (Withdrawn) The pharmaceutical composition prepared by the method of claim 17, wherein said pharmaceutical composition comprises a glutaminase-asparaginase that has been modified with succinimidyl carbonate polyethylene glycol 5000 (SC-PEG 5000), wherein said glutaminase-asparaginase is modified to an extent of from about 21% to about 49% by SC-PEG 5000, and wherein said composition prevents host-mediated inactivation.

24. (Withdrawn) The composition of claim 23, wherein said glutaminase-asparaginase is modified from about 26% to about 36% by SC-PEG 5000.

25. (Withdrawn) The composition of claim 24, wherein said glutaminase-asparaginase is modified about 31% by SC-PEG 5000.

26. (Withdrawn) The pharmaceutical composition prepared by the method of claim 17, wherein said pharmaceutical composition comprises a glutaminase-asparaginase that has been modified with mono-methoxy succinimidyl butanoate polyethylene glycol 5000 (SBA-

PEG 5000), wherein said glutaminase-asparaginase is modified from about 25% to about 58% by SBA-PEG 5000, and wherein said composition prevents host-mediated inactivation.

27. (Withdrawn) The composition of claim 26, wherein said glutaminase-asparaginase is modified from about 30% to about 40% by SBA-PEG 5000.

28. (Withdrawn) The composition of claim 27, wherein said glutaminase-asparaginase is modified about 35% by SBA-PEG 5000.

29. (Withdrawn) The pharmaceutical composition prepared by the method of claim 17, wherein said pharmaceutical composition comprises a glutaminase-asparaginase that has been modified with aldehyde polyethylene glycol 2000 (ALD-PEG 2000), wherein said glutaminase-asparaginase is modified from about 45% to about 65% by ALD-PEG 2000, and wherein said composition prevents host-mediated inactivation.

30. (Withdrawn) The pharmaceutical composition prepared by the method of claim 17, wherein said pharmaceutical composition comprises a glutaminase-asparaginase that has been modified with succinimidyl propionate polyethylene glycol 5000 (SPA-PEG 5000), wherein said modified glutaminase-asparaginase is modified from about 25% to about 65% by SPA-PEG 5000, and wherein said composition prevents host-mediated inactivation.

31. (Withdrawn) The composition of claim 30, wherein said glutaminase-asparaginase is modified from about 40% to about 55% by SPA-PEG 5000.

32. (Withdrawn) A composition comprising a glutaminase-asparaginase, wherein said glutaminase-asparaginase has been modified with succinimidyl carbonate polyethylene glycol 5000 (SC-PEG 5000) to an extent of about between 21% and 49%.

33. (Withdrawn) The modified therapeutic composition of claim 32, wherein said glutaminase-asparaginase has been modified to an extent of about between 26% and 36%.

34. (Withdrawn) The modified therapeutic composition of claim 33, wherein said glutaminase-asparaginase has been modified to an extent of about 31%.

35. (Withdrawn) A composition comprising a glutaminase-asparaginase, wherein said glutaminase-asparaginase has been modified with succinimidyl butanoate polyethylene glycol 5000 (SBA-PEG 5000) to an extent of about between 25% and 58%.

36. (Withdrawn) The modified therapeutic composition of claim 35, wherein said glutaminase-asparaginase has been modified to an extent of about 30% to 40%.

37. (Withdrawn) The modified therapeutic composition of claim 36, wherein said glutaminase-asparaginase has been modified to an extent of about 35%.

38. (Withdrawn) A composition comprising a glutaminase-asparaginase, wherein said glutaminase-asparaginase has been modified with aldehyde polyethylene glycol 2000 (ALD-PEG 2000) to an extent of about between 45% and 65%.

39. (Withdrawn) A composition comprising a glutaminase-asparaginase, wherein said glutaminase-asparaginase has been modified with succinimidyl propionate polyethylene glycol 5000 (SPA-PEG 5000) to an extent of about between 25% and 65%.

40. (Withdrawn) The modified therapeutic composition of claim 39, wherein said glutaminase-asparaginase has been modified to an extent of about 40% to 55%.

41. (Previously Presented) The method of claim 1, wherein the subject administered the first modified therapeutic agent is different from the subject administered the second modified therapeutic agent.

42. (Previously Presented) A method for determining the type of biocompatible polymer, the extent of modification, and the conditions for modification of a therapeutic agent with a biocompatible polymer to prevent host-mediated inactivation of said therapeutic agent when covalently modified by said biocompatible polymer, comprising:

(a) selecting a biological activity;

(b) assaying **a first blood sample for** the selected biological activity of step (a) of a first modified therapeutic agent after said first modified therapeutic agent has been administered to ~~a~~ **an immunocompetent** subject, wherein said first modified therapeutic agent is covalently modified with a biocompatible polymer;

(c) assaying **a second blood sample for** the selected biological activity of step (a) of said first modified therapeutic agent after at least one booster dose of said first modified therapeutic agent has been administered to said subject;

(d) assaying **a third blood sample for** the selected biological activity of step (a) of a second modified therapeutic agent after said second modified therapeutic agent has been administered to ~~a~~ **an immunocompetent** subject, wherein said second modified therapeutic agent is covalently modified with a biocompatible polymer and wherein at least one condition selected from the group consisting of the type of biocompatible polymer, the extent of modification, and the conditions for modification differs from the conditions of said first modified therapeutic agent;

(e) assaying **a fourth blood sample for** the selected biological activity of step (a) of said second modified therapeutic agent after at least one booster dose of said second modified therapeutic agent has been administered to said subject; and

(f) comparing the selected biological activity of step (a) of said first modified therapeutic agent with the selected biological activity of step (a) of said second modified therapeutic agent to select the type of biocompatible polymer, the extent of modification, and the conditions for modification that prevent host-mediated inactivation of said therapeutic agent when covalently modified by said biocompatible polymer**,**

wherein said blood samples are collected from said immunocompetent subject,

wherein said biological activity is selected from the group consisting of an enzyme catalyzing a reaction, a molecule binding a receptor or antibody, mediating a receptor-mediated response such as ion influx/efflux or generation of second messengers, antagonizing or blocking a receptor-mediated response, induction of apoptosis and release or uptake of a neurotransmitter or hormone and

wherein said assaying comprises measuring the extent to which said first modified therapeutic agent and said second modified therapeutic agent catalyze a reaction, bind a targeted receptor or antibody, or mediate activity of a receptor.

43. Cancelled.

44. (Previously Presented) A method for determining the type of biocompatible polymer, the extent of modification, and the conditions for modification of a therapeutic agent with a biocompatible polymer to prevent host-mediated inactivation of said therapeutic agent when covalently modified by said biocompatible polymer, comprising:

(a) selecting a biological activity;

(b) assaying **a first blood sample for** the selected biological activity of step (a) of a first modified therapeutic agent after said first modified therapeutic agent has been administered to ~~a~~ **an immunocompetent** subject, wherein said first modified therapeutic agent is covalently modified with a biocompatible polymer;

(c) assaying **a second blood sample for** the selected biological activity of step (a) of said first modified therapeutic agent after at least one booster dose of said first modified therapeutic agent has been administered to said subject;

(d) assaying **a third blood sample for** the selected biological activity of step (a) of a second modified therapeutic agent after said second modified therapeutic agent has been administered to ~~a~~ **an immunocompetent** subject, wherein said second modified therapeutic agent is covalently modified with a biocompatible polymer and wherein at least one condition selected from the group consisting of the type of biocompatible polymer, the extent of modification, and the conditions for modification differs from the conditions of said first modified therapeutic agent;

(e) assaying **a fourth blood sample for** the selected biological activity of step (a) of said second modified therapeutic agent after at least one booster dose of said second modified therapeutic agent has been administered to said subject; ~~and~~

(f) comparing the selected biological activity of step (a) of said first modified therapeutic agent with the selected biological activity of step (a) of said second modified therapeutic agent to determine the relative bioavailability of said first modified therapeutic agent and said second therapeutic agent**; and**

(g) selecting the type of biocompatible polymer, the extent of modification, and the conditions for modification that prevent host-mediated inactivation of said therapeutic agent when covalently modified by said biocompatible polymer based upon the comparison of step (f)**.**

wherein said blood samples are collected from said immunocompetent subject,

wherein said biological activity is selected from the group consisting of an enzyme catalyzing a reaction, a molecule binding a receptor or antibody, mediating a receptor-mediated response such as ion influx/efflux or generation of second messengers, antagonizing or blocking a receptor-mediated response, induction of apoptosis and release or uptake of a neurotransmitter or hormone and

wherein said assaying comprises measuring the extent to which said first modified therapeutic agent and said second modified therapeutic agent catalyze a reaction, bind a targeted receptor or antibody, or mediate activity of a receptor.

45-46. Cancelled.